EXHIBIT II

IND SUBMISSION

February 28, 1997

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Central Document Room
12229 Wilkins Avenue
Rockville, Maryland 20852
Attn: Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products

SCH 58235
Capsules
Serial No.: 000

SUBJECT: INVESTIGATIONAL NEW DRUG APPLICATION

Dear Dr. Sobel:

Enclosed herein is an Investigational New Drug Application for SCH 58235 Capsules.

SCH 58235 is an azetidinone inhibitor of intestinal absorption of cholesterol that is being studied for treatment of primary hypercholesterolemia. The drug is structurally related to SCH 48461, for which relevant activity has been previously shown (IND 42075) but is more potent and thus far, has a safe profile in nonclinical studies, in doses smaller than SCH 48461. No unwanted pharmacologic effect has yet been observed nor has any particular target organ of toxicity been identified.

The first two clinical trials with SCH 58235 - randomized, double-blind studies of tolerability and pharmacokinetics associated with single or multiple doses taken orally following an overnight fast - have recently completed. Preliminary safety results from both studies and a preliminary evaluation of pharmacokinetics from the single-dose study are presented in section nine of this submission.

Based on preclinical safety studies the preliminary results of the rising single and rising multiple dose safety tolerability and pharmacokinetics, the sponsor is opening the IND with a Pilot Dose Ranging Study of the Safety and Efficacy of SCH 58235 Compared to Placebo and Lovastatin in Patients with Primary Hypercholesterolemia.

Should you have any questions concerning this submission, please contact Ms. Mary Jane Boyle at (908) 298-5693.

Please be advised that material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,

Joseph F. Lamendola, Ph.D.
Vice President
U.S. Regulatory Affairs

MJB/pjm
Enclosures

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014
Expiration Date: November 30, 1995.
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. NAME OF SPONSOR
Schering Corporation

2. DATE OF SUBMISSION
February 28, 1997

3. ADDRESS *(Number, Street, City, State and Zip Code)*
2000 Galloping Hill Road
Kenilworth, New Jersey 07033

4. TELEPHONE NUMBER *(Include Area Code)*
(908) 298-2628

5. NAME(S) OF DRUG *(Include all available names: Trade, Generic, Chemical, Code)*
SCH 58235 CAPSULES

6. IND NUMBER *(If previoulsy assigned)*

7. INDICATION(S) *(Covered by this submission)*
Hypercholesterolemia

8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED ☐ PHASE 1 ■ PHASE 2 ☐ PHASE 3 ☐ OTHER _____ *(Specify)*

9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS *(21 CFR Part 312)*, NEW DRUG OR ANTIBIOTIC APPLICATIONS *(21 CFR Part 314)*, DRUG MASTER FILES *(21 CFR 314.420)*, AND PRODUCT LICENSE APPLICATIONS *(21 CFR Part 601)* REFERRED TO IN THIS APPLICATION
None

10. *IND submissions should be consecutively numbered. The initial IND should be numbered "Serial Number: 000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 001." Subsequent submissions should be numbered consecutively in the order in which they are submitted.*

SERIAL NUMBER: 0 0 0

11. THIS SUBMISSION CONTAINS THE FOLLOWING: *(Check all that apply)*

■ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND)
☐ RESPONSE TO CLINICAL HOLD

PROTOCOL AMENDMENT(S):
☐ NEW PROTOCOL
☐ CHANGE IN PROTOCOL
☐ NEW INVESTIGATOR

INFORMATION AMENDMENT(S):
☐ CHEMISTRY / MICROBIOLOGY
☐ PHARMACOLOGY / TOXICOLOGY
☐ CLINICAL

IND SAFETY REPORT(S):
☐ INITIAL WRITTEN REPORT
☐ FOLLOW-UP TO A WRITTEN REPORT

☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE

☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED. ☐ OTHER _____ *(Specify)*

CHECK ONLY IF APPLICABLE

A JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.

☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(c) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR 312.7(d)

FOR FDA USE ONLY

CDR/DBIND/OGD RECEIPT STAMP	DDR RECEIPT STAMP	IND NUMBER ASSIGNED:
		DIVISION ASSIGNMENT:

CONTENTS OF APPLICATION

This application contains the following items: *(check all that apply)*

- ■ 1. Form FDA 1571 *[21 CFR 312.23 (a) (1)]*
- ■ 2. Table of contents *[21 CFR 312.23 (a) (2)]*
- ■ 3. Introductory statement *[21 CFR 312.23 (a) (3)]*
- ■ 4. General investigational plan *[21 CFR 312.23 (a) (3)]*
- ■ 5. Investigator's brochure *[21 CFR 312.23 (a) (5)]*
- 6. Protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ■ a. Study protocol(s) *[21 CFR 312.23 (a) (6)]*
  - ☐ b. Investigator data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23 (a)(6)(iii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23 (a) (6)(iii)(b)]* or completed Form(s) FDA 1572
- ■ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23 (a) (7)]*
  - ■ Environmental assessment or claim for exclusion *[21 CFR 312.23 (a) (7)(iv)(e)]*
- ■ 8. Pharmacology and toxicology data *[21 CFR 312.23 (a) (8)]*
- ■ 9. Previous human experience *[21 CFR 312.23 (a) (9)]*
- ☐ 10. Additional information *[21 CFR 312.23 (a) (10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ■ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ■ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Cynthia Cuffie, M.D.
Distinguished Clinical Research Physician
Cardiovascular, Dermatology, Endocrinology

15. NAME(S) AND TITLE(S) OF THE PERSON(S) RESPONSIBLE FOR REVIEW AND EVALUATION OF INFORMATION RELEVANT TO THE SAFETY OF THE DRUG

Robert J. Spiegel, M.D.
Senior Vice President
Worldwide Clinical Research

I agree not to begin clinical investigations until 30 days after FDA's receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.

16. NAME OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	17. SIGNATURE OF SPONSOR OR SPONSOR'S AUTHORIZED REPRESENTATIVE	
Joseph F. Lamendola, Ph.D. Vice President, U.S. Regulatory Affairs		
18. ADDRESS *(Number, Street, City, State and Zip Code)*	19. TELEPHONE NUMBER *(Include Area Code)*	20. DATE
2000 Galloping Hill Road Kenilworth, New Jersey 07033	(908) 298-2628	2/28/97

(WARNING: A willfully false statement is a criminal offense U S C Title 18, Sec. 1001)